## REMARKS

Claims 31-39 and 42 are pending.

Claims 31-39 and 42 are rejected under 35 U.S.C. §103(a) as being unpatentable over Chen *et al.*

Chen teaches vitamin $D_3$ compounds with a C(20) methyl in the natural configuration. In contrast, the compounds in the instant invention are C(20)-dimethyl vitamin $D_3$ analogues. The Examiner has rejected the instant claims as homologs of the compounds disclosed in the Chen reference.

Applicants believe that the characterization of the instant compounds as mere homologs is both scientifically erroneous and results in an incorrect 35 U.S.C. §103(a) analysis. Moreover, the courts have long recognized that homology does not *per se* render a compound obviousness over prior art.

> So it is that while this court has found the prior art disclosure of homologues of compounds to render prima facie obvious claims to compounds, homology should not be automatically equated with *prima facie* obviousness...
>
> This court has said that "all disclosures in a reference must be evaluated for that they fairly teach one of ordinary skill in the art."

*In re Langer and Haynes* 465 F.2d 896, 175 USPQ. 169 (CCPA. 1972),

Even if the instant compounds can be considered homologs, the biological properties are sufficiently unpredictable that there is can be no expectation that the compounds comprising the present invention will have any activity, much less improved properties relative to compounds in the prior art.

Homology is a loosely used, but seldom rigorously defined, term. While structurally it has been defined as "[a] series of organic compounds in which each successive member has one more $CH_2$ group in its molecule than the preceding member. For instance $CH_3OH$ (methanol), $C_2H_5OH$ (ethanol), $C_3H_7OH$ (propanol), etc., form a homologous series" (N.I. Sax and R.J. Lewis Sr. *Hawleys Condensed Chemical Dictionary,* 11th edition, van Nostrand Reinhold, New York 1987 p.607). However, the position where the extra methylene is inserted makes a significant difference in the chemical properties, e.g. $C_2H_5OH$ (ethanol) vs $CH_3OCH_3$ (dimethyl ether)

Roberts and Caserio's organic chemistry text emphasizes the limits of predictions based simply on the number of atoms in a series of compounds.

> Members of a group of compounds with similar chemical structures and graded physical properties and which differ from one another by the number of atoms in the structural backbone, such as *n*-alkanes, are said to constitute a homologous series. ... Branched chain alkanes do not exhibit the same smooth gradation in physical properties as the *n*-alkanes. Usually there is too great a variation in molecular structure for regularities to be apparent.

J.D. Roberts and M. Caserio, *Basic Principles of Organic Chemistry* W.A. Benjamin, New York 1984, pp70-71, emphasis added).

The variation in physical properties when branching is added to an alkane does not follow the simple trends observed in a series of *normal* alkanes. Extending this analogy to biological structure activity relationship strains all credibility. Even in well studied classical neurotransmittors, adding a simple methyl can alter the observed behavior. For example, the β-adrenergic agonists epinephrine (Epi) and norepinephrine (NE) which differ structurally by only an secondary N-methyl amine *vs.* a primary amine completely reverse their relative potency for β-adrenergic subtypes: $\beta_2$ Epi>>NE, $\beta_1$Epi=NE, $\beta_3$ NE>>Epi. (B. H. Hoffman, R. L. Lefkowitz and P. Taylor, Neurotransmission. In Goodman & Gilman's *The Pharmacological Basis of Therapeutics*, 9th Edition; J. G. Hardman and L. E. Limbird, Eds-in Chief.; McGraw-Hill: New York, 1996, p. 125)

The compounds of the present invention differ from the prior art compounds by a single one carbon atom. That additional carbon atom converts the C-20 tertiary carbon to a quaternary center. This change significantly alters the conformation of that C-17 side-chain and, therefore, its ability to interact with a biological receptor and induce a biological response (*infra*). Predictions based on chemical homology are of little value when even small structural change can significantly alter conformation and/or electronic properties of a portion of a molecule that interacts with a receptor.

The configuration of C-20 methyl has been found to alter the ligand-bound conformation of vitamin $D_3$ analogs. Tocchini-Valentini *et al.* (*Proc. Nat. Acad. Sci. USA* **2001** 98(10):5491-95) have described X-ray structures of C-20 *epi* vitamin $D_3$ compounds and found significant differences in the chain conformation. This C-20 *epi* analog was found to be a potent growth inhibitor and inducer of cell differentiation while

showing affinity similar to vitamin $D_3$ for the vitamin D receptor and exhibited decreased hypercalcemic side effects. This confirmed earlier reports Binderup *et al.* (*Biochem. Pharmacol.* **1991** 42(8):1569-1575) that the unnatural *epi*-C(20) compound was as much as 100 times more potent then the corresponding natural isomer.

In the cited Chen reference only the naturally occurring C(20) methyl configuration is disclosed. Structural variation at that position can dramatically alter bioactivity (*supra*) and the instant compounds contain additional steric requirements absent in the prior art compounds. The Chen reference does not teach the treatment of osteoporosis or hyperparathyroidism. The Chen reference teaches vitamin $D_3$ analogues which modulate cell proliferation or cell differentiation of keratinocytes which is relevant to the treatment of skin diseases, especially psoriasis. The Chen reference also teaches inhibition of cell proliferation by HL-60 leukemia cells which is relevant to cancer. The Chen reference further teaches regulation of calcium absorption but intestinal cells and bone mobilization in vitamin $D_3$ deficient mice. Increases in calcium absorption are indicative of potential hypercalcemia, a toxic side effect. Mobilization of calcium from the bone is counterproductive in the treatment of osteoporosis. Neither property is indicative of successful treatment of osteoporosis. The reference does not teach or suggest that a quaternary C(20) position is useful or beneficial and therefore there is no expectation that the instant compounds will have beneficial properties.

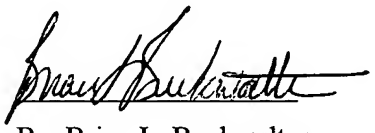
The most reliable analogy for the instant C(20)-dimethyl compounds are the corresponding C(20)-cyclopropyl analogs which were encompassed in the generic formula in the grandparent case, now U.S. Patent No. 6,492,353. The steric profile of the allowed C(20)-cyclopropyl most closely resembles the instant compounds and any electronic properties unique to the cyclopropyl ring would not likely alter the receptor interactions. The specification discloses the advantage of C(20) quaternary compounds, albeit C(20) cyclopropyl derivatives which Applicant believes are the best analogy to the instant compounds. The specification demonstrates that C(20) quaternary compounds are significantly better than vitamin $D_3$ analogs in promoting bone calcium accretion (Example 11, p.48).

The asserted *prima facie* rejection is based inappropriate scientific rationale that is not required by precedent or case law. Applicants respectfully request reconsideration and withdrawal of the previous rejection and issuance of a notice of allowance.

## CONCLUSIONS

For the reasons herein disclosed the claims as amended are believed to be in condition for allowance. A petition for a three month extension of time is enclosed herewith. The Examiner is authorized to deduct the fee under 37 CFR 1.17(a)(3) from deposit account 18-1700. No other fees are believed to be due with this submission but in the event that a fee is required the Examiner is authorized to deduct it from the deposit account. If the Examiner believes a telephone conference will expedite the prosecution of this application, the Examiner is invited to contact the undersigned at the number indicated below.

Respectfully submitted,



By: Brian L. Buckwalter
Registration No. 46,585
Agent for Applicant

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Roche Palo Alto LLC
3431 Hillview Avenue,
Palo Alto, CA 94304-1397
Telephone 650-855-6995
Telecopier 650-855-5322

Enc: